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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,797	BRIGHAM ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37,39-41 and 54-59* is/are pending in the application.

4a) Of the above claim(s) *55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,37,39-41,54,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed 10-13-05 has been entered. Claim 38 has been canceled. Claims 58 and 59 have been added. Claims 1, 37, 39-41 and 54-59 are pending. Claims 1, 37, 39-41, 54, 58 and 59 are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 37, 39-41 and 54 remain rejected and claim 59 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing endotoxin induced increase in pulmonary vascular resistance (PVR) by intravenously administering DOTMA/DOPE liposome complexed PCMV4AAT, which expresses alpha1 antitrypsin, into piglets as compared to intravenously administered recombinant alpha1 antitrypsin into piglets, does not reasonably provide enablement for enhancing delivery of alpha1 antitrypsin by administering any vector expressing alpha1 antitrypsin via various administration routes, wherein the blood concentration of alpha1 antitrypsin encoded by the nucleic acid displayed an enhanced alpha1 antitrypsin activity as compared to the same blood level of administered recombinant alpha1 antitrypsin protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the

preceding Official action mailed 6-25-04. Applicant's arguments filed 10-13-05 have been fully considered but they are not persuasive.

Applicants argue that Figure 2 shows a marked decrease in PVR in the piglets given alpha1 antitrypsin nucleic acid compared to piglets given recombinant alpha1 antitrypsin protein. Applicants further argue that Figure 1 shows significant inhibition of RSV replication by AAT gene delivery as compared to AAT protein administration (amendment, p. 4-5). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 6-25-04. The claims read on an alpha1 antitrypsin encoded by the nucleic acid has enhanced alpha1 antitrypsin activity as compared to a recombinant alpha1 antitrypsin protein under the same blood concentration in a subject. Although there is a marked decrease in PVR in the piglets given alpha1 antitrypsin nucleic acid compared to piglets given recombinant alpha1 antitrypsin protein, however, there is no evidence that shows the alpha1 antitrypsin encoded by the nucleic acid has enhanced alpha1 antitrypsin activity than a recombinant alpha1 antitrypsin. The alpha1 antitrypsin encoded by the nucleic acid should be the same as a recombinant alpha1 antitrypsin protein. It is unclear how one would have an enhanced activity than the other. The reason for the marked decrease in PVR in the piglets having gene delivery of alpha1 antitrypsin could be due to sufficient amount of nucleic acid encoding the alpha1 antitrypsin protein at the target lung cells and higher amount of alpha1 antitrypsin is expressed at said target lung cells as compared to recombinant alpha1 protein delivery. The specification points out that there is difficulty in direct delivery of the recombinant alpha1 antitrypsin to lung cells for treating AAT related disorders (see specification, p. 3-4). Although the blood level of the recombinant alpha1 antitrypsin could be the same or much higher, e.g. 50-100 times, than the alpha1 antitrypsin encoded by the

nucleic acid in a subject, however, it is not necessary that there would be sufficient recombinant alpha1 antitrypsin protein at the target lung cells to reduce the endotoxin induced PVR. This point is further strengthened by applicants' own remarks on page 6, lines 4-8, of the amendment filed 10-13-05. The alpha1 antitrypsin encoded by the nucleic acid measured in the blood could be the expressed alpha1 antitrypsin released from the target lung cells. Similarly, the difference in the inhibition of RSV replication could be due to the difference in the amount of expressed alpha1 antitryposin from nucleic acid and the recombinant alpha1 antitrypsin protein in the target cells.

Applicants argue that gene delivery of an alpha1 antitrypsin gene shows expression of alpha1 antitrypsin protein at the target nasal mucosa cells (amendment, p. 6, middle paragraph). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 6-25-04 and the reasons set forth above. The alpha1 antitrypsin encoded by the nucleic acid should be the same as a recombinant alpha1 antitrypsin protein. It is unclear how one would have an enhanced activity than the other. The reason for the marked decrease in PVR via gene delivery of alpha1 antitrypsin nucleic acid as compared to alpha1 antitrypsin protein delivery could be that there is more alpha1 antitrypsin protein present at the target cells via gene delivery than protein delivery. The specification fails to provide adequate guidance for the correlation between enhanced delivery of alpha1 antitrypsin to a respiratory cell and enhanced antitrypsin activity of nucleic acid encoded antitrypsin. There is no evidence of record that a nucleic acid encoded antitrypsin that shows enhanced antitrypsin activity would result in enhanced delivery of antitrypsin to a respiratory cell in a subject.

Applicants cite Gautam (Exhibit A) and argue that it was well known in the art to use viruses as vectors for gene therapy and the specification discloses various methods of administration for gene delivery. Applicants further argue that Gautam discloses intratracheal or intranasal instillation for gene delivery to lungs and the specification teaches intravenous administration and delivery to the nasal epithelium in humans, therefore, one of ordinary skill in the art would be able to make and use the claimed invention (amendment, p. 6-7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 6-25-04. The specification only discloses liposome-mediated gene transfer. The claims encompass the use of various vectors expressing alpha1 antitrypsin via various administration routes to a subject for enhancing delivery of alpha1 antitrypsin to a respiratory cell in a subject. Although it was known to make and use viruses or other type of vector for gene delivery in vivo, but the vector used and the administration route play important roles in determining the efficiency of gene transfer in vivo. The use of viruses (viral vectors) is powerful technique, however, humans have an immune system to fight off the virus. The fate of the DNA vector, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell are all important factors for a successful gene delivery. One might expect high gene delivery efficiency via direct administration, such as intratracheal or intranasal instillation, however, there is no evidence of record that demonstrates gene delivery of a nucleic acid encoding alpha1 antitrypsin in various vectors via various administration routes, such as oral administration,

subcutaneous administration, or intramuscular administration, would enhance delivery of alpha1 antitrypsin to a respiratory cell in a subject as compared to protein delivery or to provide sufficient amount of expressed alpha1 antitrypsin protein at target cells to decrease PVR in a subject.

Applicants argue that the alpha1 antitrypsin gene is expressed for a long enough period of time at adequate levels in a significant population of cells and the respiratory cells expressed alpha1 antitrypsin after transfection. Applicants further argue that the invention provides a significant advance in targeting strategy compared to cited references Verma and Eck, and Verma and Eck are not clearly relevant to the claimed invention (amendment, p. 8-9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 6-25-04 and the reasons set forth above. The cited references Verma and Eck discuss the difficulties encountered in gene delivery in vivo via various vectors and administration routes, and the factors that would affect the efficiency of gene delivery in vivo. The instant invention encompasses gene delivery through the use of various vectors and administration routes, therefore, the cited references Verma and Eck are relevant to the instant invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: whether the alpha1 antitrypsin is delivered to the respiratory

cell in the subject. The method step fails to refer back to the preamble of the claimed method, i.e. delivery of alpha1 antitrypsin to a respiratory cell in a subject. Applicants' amendment filed 10-13-05 necessitates this new ground of rejection.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claim 58 is rejected under 35 U.S.C. 102(e) as being anticipated by Brantly et al., 1995 (US Patent No. 5,439,824). Applicants' amendment filed 10-13-05 necessitates this new ground of rejection.

Claim 58 is directed to a method for delivering alpha1 antitrypsin to a respiratory cell in a subject by administering a nucleic acid molecule encoding alpha1 antitrypsin to the subject and the subject displays an enhanced blood concentration of alpha1 antitrypsin encoded by the nucleic acid compared to a subject not exposed to said nucleic acid.

Brantly teaches preparation of plasmid pPI-MG2 containing the nucleotide sequence encoding alpha1 antitrypsin (AAT) and intron II of AAT gene and preparation of a retroviral vector comprising the MG2 construct (e.g. Experiment II, VII). Brantly teaches using MG II construct in a retroviral vector or an adenoviral vector to treat ATT deficiencies in the lung of

patient and predicts uptake of ATT expression vector in alveolar cells and ATT could be expressed in said alveolar cells (e.g. Experiment IX). Since the introduced ATT would be expressed in alveolar cells, it is expected that the expressed ATT would be secreted into blood stream and it is inherent that blood concentration of ATT in a subject would be higher than that of a subject not exposed to the nucleic acid encoding ATT. Thus, claim 58 is anticipated by Brantly.

7. Claim 58 is rejected under 35 U.S.C. 102(b) as being anticipated by Canonico et al., 1994 (American Journal of Respiratory Cell and Molecular Biology, Vol. 10, No. 1, p. 24-29). Applicants' amendment filed 10-13-05 necessitates this new ground of rejection.

Claim 58 is directed to a method for delivering alpha1 antitrypsin to a respiratory cell in a subject by administering a nucleic acid molecule encoding alpha1 antitrypsin to the subject and the subject displays an enhanced blood concentration of alpha1 antitrypsin encoded by the nucleic acid compared to a subject not exposed to said nucleic acid.

Canonico teaches preparation of a plasmid containing human ATT gene under the control of CMV promoter complexed to cationic liposomes, and said complexed plasmid-liposome was delivered to New Zealand White rabbits intravenously or by aerosol. Canonico shows that intravenous administration results in halpha1AT (hATT) expression in the pulmonary endothelium and the airway epithelium, and aerosol administration results in ATT expression in alveolar epithelial cells and airway elithelium (e.g. abstract). It is expected that the expressed ATT would be secreted into blood stream and it is inherent that blood concentration of ATT in a

subject would be higher than that of a subject not exposed to the nucleic acid encoding ATT. Thus, claim 58 is anticipated by Canonico.

Conclusion

No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER